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Title: GLYCEROL AS A PREDICTOR...

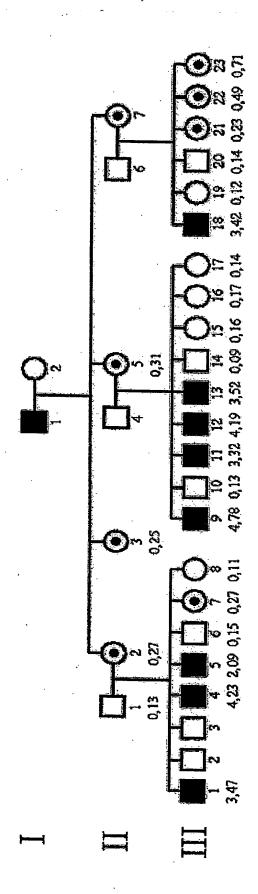
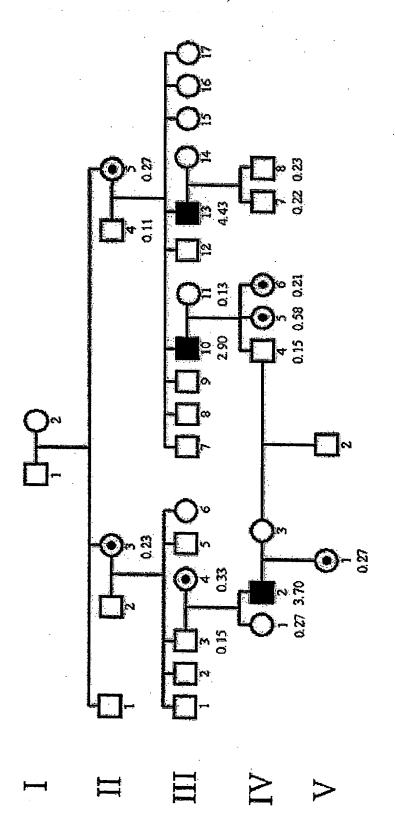
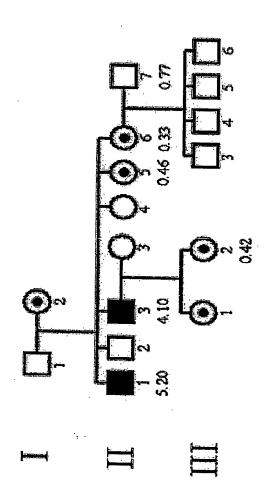


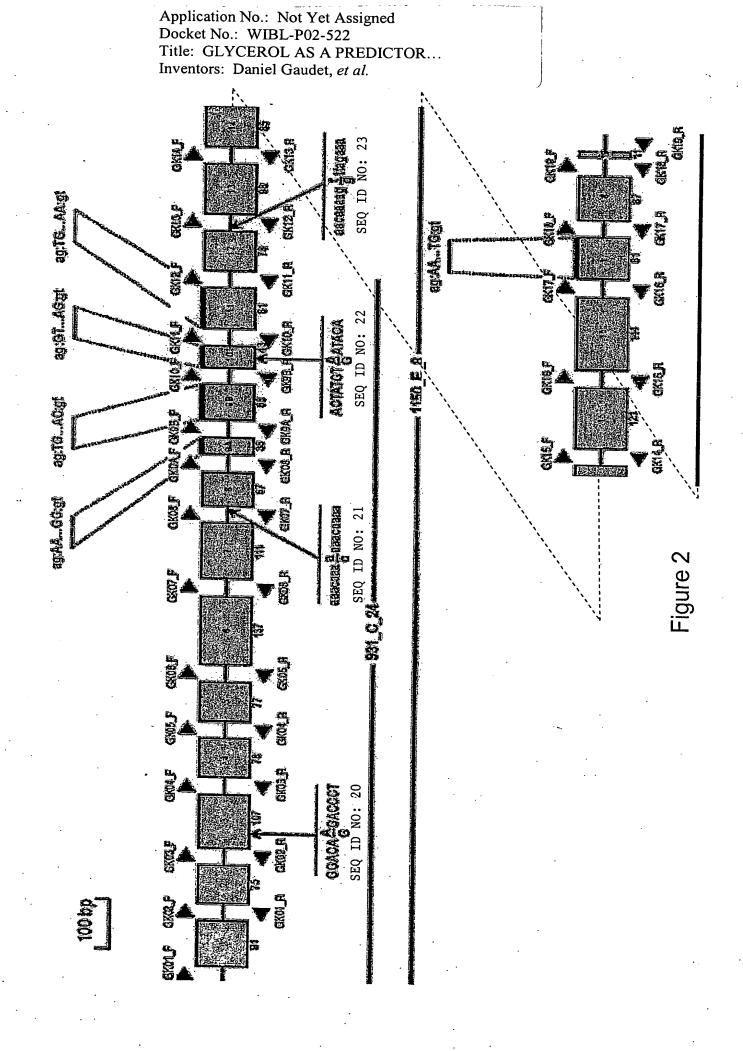
Figure 1A

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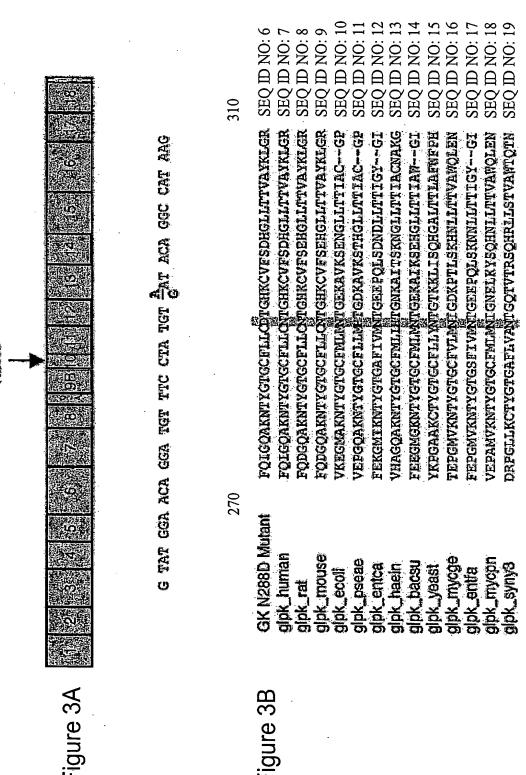
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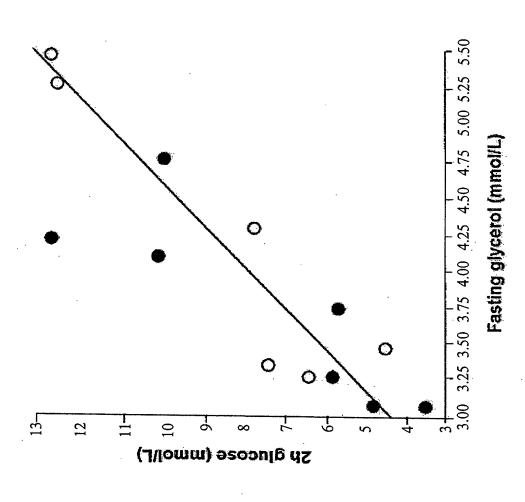


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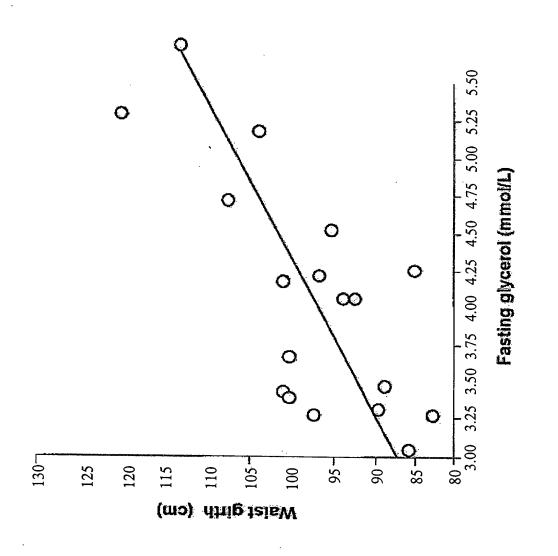
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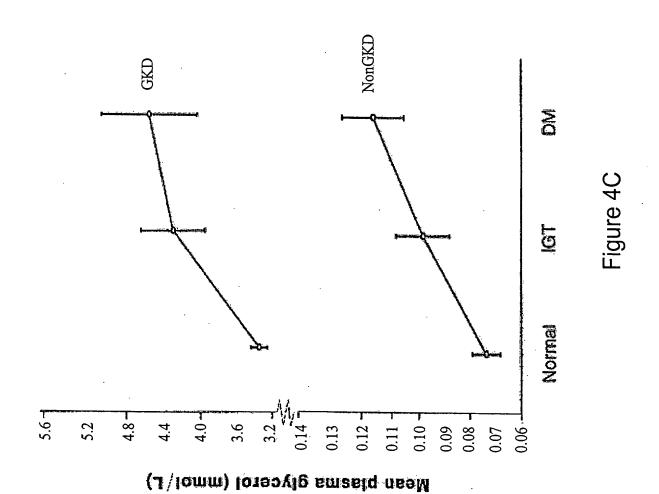


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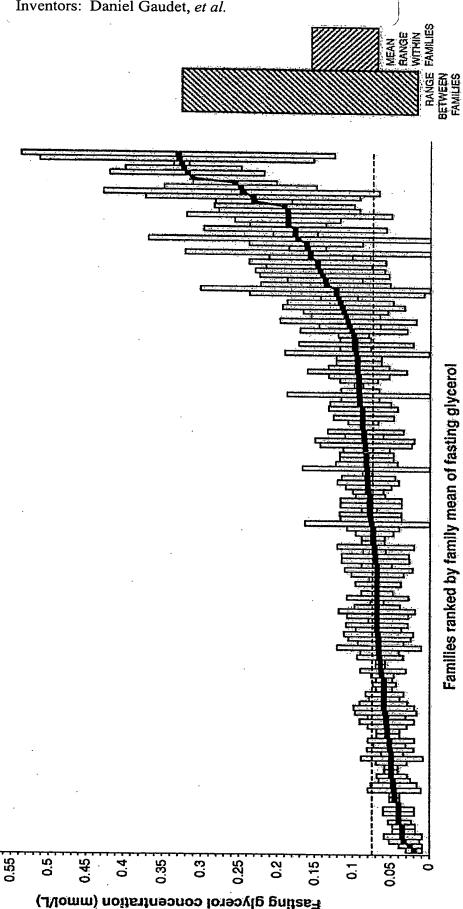


Figure 5

Docket No.: WIBL-P02-522

Title: GLYCEROL AS A PREDICTOR...

Inventors: Daniel Gaudet, et al.

poly: A/G

location:13th base of exon 3

ATGCCTTCTTTTGTCAAAGATGGGTGGAACA[A/G]GACCCTAAGGAAATTCTACAT
TCTGTCT SEQ ID NO: 1

CAA vs CAG ==> silent

poly: A/C

location:17th base of intron 8

TAATGGTAAAAAACAAACAAA [A/C] AAACAAAAAACACACCAAAAAAACCAA

SEQ ID NO: 2

poly: A/G

location: 29th base of exon 10

TTCATTCTCCCTTCAACCATAGGTATGGAACAGGATGTTTCTTACTATGT [A/G]AT

ACAGGCCATAAGGTtGGTTTTTAATAAAAATGATTAAGTCA

SEQ ID NO: 3

AAT vs GAT ==> N to D

poly: G/T

location: 22nd base of intron 12

 ${\tt GAAATTGGTGAGTGTTCTAACAAAAG~[G/T]~TTAGAAAATCTGAAAAATGACACA}$ 

TTTCA SEQ ID NO: 4

Docket No.: WIBL-P02-522

Title: GLYCEROL AS A PREDICTOR...

Inventors: Daniel Gaudet, et al.

### SEQ ID NO: 5

#### Exon 1:

#### Exon 2:

#### Exon 3:

CAATGCCTTCTTTTGTCAAAGATGGGTGGAACA [A/G] GACCCTAAGGAAATTCTACATTCT GTCTATGAGTATAGAGAAAACATGTGAGAAACTTGGACAGCTCAATATTGATATTTCCAA CATAAAAGGTATTTTAGTAGAAATATTTTACCCACA

#### Exon 4:

TGTAAAACGACGGCCAGTTGAGAGCTGTTTTCCTGAAGTAGTTCCTACTTGTTAAATTTTTG ACTTCCTTCTGTTTAACTTTCTCTTTAAAGCTATTGGTGTCAGCAACCAGAGGGAAACCACT GTAGTCTGGGACAAGATAACTGGAGAGCCTCTCTACAATGCTGTGGGTAAGCTGTCATGCAT GGATGTCAAATGTAGGGCCTTTCTTCACATTGCAA

#### Exon 5:

#### Exon 6:

Docket No.: WIBL-P02-522

Title: GLYCEROL AS A PREDICTOR...

Inventors: Daniel Gaudet, et al.

#### Exon 7:

TGTAAAACGACGGCCAGTTGTGCTCTGCTGATTATGACCCTTAACAATATGTAAATTAAATT GCCAATAAGTACAAATTTAACCTGATTTTTTTACTCTGCCTAGAGTTTGACAGGAGGAGTCA ATGGAGGTGTCCACTGTACAGATGTAACAAATGCAAGTAGGACTATGCTTTTCAACATTCAT TCTTTGGAATGGGATAAACAACTCTGCGAGTAAGTTCTGTTTTTGCTCTAAATATAGTTTTCC CAATACACTACCTATTTATAACCGAAATCTTAATATTTTCAGATGTCAGTGGAGCA

#### Exon 8:

## Exons 9A and 9B

# Exons 10 and 11:

TTATTTGCTTTCAATAAAATTGTCTTCTATTCATTCTCCCTTCAACCATAGGTATGGAACAG GATGTTTCTTACTATGT [A/G] ATACAGGCCATAAGGTTGGTTTTTTAAATTAAAAAATTGA TTTAAAAGTCTAAGTTCATCTAAATAATGCTTGAACATAATTTACTATTAAACAACTTTTAG  ${ t TCTTTAGCTTTACTTAATCTTTATCAGGGTTTAATTTAGAGCTCAATACAAAATTTGAATC$ GTTCTAATAAGAACCATTTTAGACTCTTTGAATTTTATATGTGTGTTTTTAATTGTGCTGGG GGGAAATCTAGACTGAGACCTCATCAAATTCTTAATGCAAATCTAATTTGAAACAAGGAATA ATTTTCTGATCATGGCCTTCTCACCACAGTGGCTTACAAACTTGGCAGAGACAAACCAGTAT ATTATGCTTTGGAAGTAAGTTCTTTTTAATCAATATGGATAATATGACAAACATTCAAAGCT AATAAAATCACAGAGTTTTCTAACACTTTTCTGGTAAATCTTAATACAGAGGACTCAAAAA GTTCTGCTTTCTTGGCATTTGATTGAGTTGAAGGAACCTGAAACTGATCTGGGTGTCAGGAC TCACAGGAGACCTTGATTAGATTGGTTCCTCAGTTCTTATGCCAATTAATCATGTCACCTTA TGCTCCAGTGTTCCAAAGAGAACCCTGGGCACAAATAGGCAGAACAACTCTCTTCACTTGTC CCACTTATCACTGGAAACATTTGTTTCAAACATTTTTGTATGTTATAGTAGGAATATGCCAG CCTAAGCCTATA

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Title: GLYCEROL AS A PREDICTOR...

Inventors: Daniel Gaudet, et al.

#### Exon 12:

#### Exon 13

# Exons 14 and 15:

TGTAAAACGACGGCCAGTTGATTATGTCCAATTTTCTCTTCTGGACATTTCTGTCTACCAA ATTTGACCTTTTCATATTTGAGATATTTCAAATTGATTGGTTTATATCATTCTAATCTGAAA TGCTTTTGCTGCATTAGAAGCTGTTTGTTTCCAAACTCGAGAGGTAACAAATATGGGCCTGT TTTCTTGTACTTAGTTCACTTTTATCACTCTTAAGTTATATGTTAACACCCGAGATTTATTC AGTACTGAAAATGTAGTTAATCAAATATTAAGGCTGCCTAAATACTAATCTAAATATAAGCA  ${\tt GGGTTTTCCCCCTTTTTCCAGCTGTCATTACCTTCTAAGTTCCTGTTCCCTGTCAGGCACTG}$ GGAAATTTATGGTTGTGGGGAGGCTGAGTGGCACACATTAGGCAAAGGAAACAGCACAAACA TAGGCATCaAGGCAGAAAAACAGGGTGCAAAATAGAGTTGTATAGCTTAGCTGAATATCAAG  $\tt GTGAATGCAGAGGTGTAGTGAGAGAAAAGGTTGGCTGTGACCAGATCAAAGAGGGCTTAGAA$ GACCAGAATAAGAAGTCTCAATTTATTCCATAGGCTCTTGGAAGCTCTTGAGAGTTTCTGAG  ${\tt TGGAGGATTTCAGAGATGTTACTATGAAATAGATTTATAACATTAATTGCACTGG}$ TTTATTTAAGATTTTGGATGCCATGAATCGAGACTGTGGAATTCCACTCAGTCATTTGCAGG TAGATGGAGGAATGACCAGCAACAAAATTCTTATGCAGCTACAAGCAGACATTCTGTATATA TAGTTCTTTGGG

#### Exon 16:

#### Exon 17:

Docket No.: WIBL-P02-522

Title: GLYCEROL AS A PREDICTOR...

Inventors: Daniel Gaudet, et al.

#### Exon 18:

# Exon 19:

AAAATTACTGGCTTAAATGGAAATGATGCTTCTTATTCTGTATGTTCCCATGAAAGTGAAAC TTAAAAAAAAATTCATGATTAGGGTTTCATGAAAAGGCCTTGTTTCTATGAAAATTGAGAC AGGTTGCATCTCTAAAGCTAAAAGATGGGCTATGTGTCTAGAGTCTTAGACTTCTAAAATG CATGTGGTCACTATATGTAGGTTATCTCTTCGGTGACATACACTGCAATTTGAGAGGGCTGG AAATTGTTTGCCTTGGTAAACGATTAGCAACAGTGGCAATATTTGTTAATTTTGGAATTGGC CCTGTTTGTTGCATTTTAATTGTGAGGCATGATTTAGAAATCATATGGACTTTCTAGCTTAA TAAATGATTGAATCATCTGCATTGCTTTAACTCCTGAATTGTATGCATGTATTATTGACATA TATGGTTTTTGTTCCCCATTTCAGGTATTCCATAAAACCTACCAACTCATGGATTCCCAAGA TGTGAGCTTTTTACATAATGAAAGAACCCAGCAATTCTGTCTCTTAATGCAATGACACTATT  ${\tt CATAGACTTTGATTTATTATAAGCCACTTGCTGCATGACCCTCCAAGTAGACCTGTGGCT}$ TAAACATCCACAGTTAAGGTTGGGCCAGCTACCTTTGGGGCTGACCCCCTCCATTGCCATAA CATCCTGCTCCATTCCCTCTAAGATGTAGGAAGAATTCGGATCCTTACCATTGGAATCTTCC ATCGAACATACTCAAACACTTTTGGACCAGGATTTGAGTCTCTGCATGACATATACTTGATT AAAAGGTTATTACTAACCTGTTAAAAATCAGCAGCTCTTTGCTTTTAAGAGACACCCTAAAA  $\tt GTCTTCTTTTCTACATAGTTGAAGACAGCAACATCTTCACTGAATGTTTGAATAGAAACCTC$ TACTAAATTATTAAAATAGACATTTAGTGTTCTCACAGCTTGGATATTTTTCTGAAAAGTTA TTTGCCAAAACTGAAATCCTTCAGATGTTTTCCATGGTCCCACTAATTATAATGACTTTCTG CTTTGTATGTATAACATACATGCCTATATATTTTATACACTGAGGGAGCCCATTTATAAATA AAGAGCACATTATATTCAGAAGGTTCTAACAGGG

Application No.: Not Yet Assigned Docket No.: WIBL-P02-522 Title: GLYCEROL AS A PREDICTOR... Inventors: Daniel Gaudet, et al.

|  |                   | Men                  |         |                   | Women                |         |
|--|-------------------|----------------------|---------|-------------------|----------------------|---------|
|  | N288D<br>carriers | Unaffected relatives | đ       | N288D<br>carriers | Unaffected relatives | ď       |
| Z  | 18                | 18                   |         | 14                | 14                   |         |
| Age (years)                                      | 46.4±14.2         | 42.0±18.8            | 0.32    | 44.9±13.5         | 43.7±17.8            | 0.87    |
| Uncorrected triglyceride (mmol/L) <sup>(1)</sup> | 6.26±1.13         | 2.05±0.54            | <0.0001 | 2.84±1.20         | 1.30±0.65            | 0.0002  |
| Glycerol (mmol/L)                                | 3.99±0.71         | 0.10±0.04            | <0.0001 | $0.54\pm0.14$     | 0.10±0.02            | <0.0001 |
| Corrected triglyceride (mmol/L) <sup>(1)</sup>   | 2.27±0.75         | 1.95±0.53            | <0.0001 | 2.31±1.22         | 1.19±0.67            | 0.03    |
| Free fatty acid (mmol/L)                         | $0.77\pm0.22$     | 0.57±0.25            | 0.01    | 1.29±0.35         | 0.76±0.17            | 0.0004  |
| Fasting glucose (mmol/L)                         | 5.2±0.74          | 4.8±0.31             | 0.13    | 5.0±0.7           | 4.6±0.3              | 0.10    |
| 2h glucose following OGTT (mmol/L)               | 7.9±3.1           | 5.8±1.6              | 0.02    | 7.0±6.1           | 5.0±2.1              | 0.04    |
| Fasting insulin $(mU/L)^{(1)}$                   | 13.3±14.0         | 15.1±14.8            | 0.62    | 12.2±13.1         | 9.0±3.4              | 09.0    |
| Waist girth (cm)                                 | 97.7±9.3          | 88.1±12.3            | 0.01    | 88.5±3.8          | 79.8±5.8             | 0.03    |
| Body mass index $(kg/m^2)$                       | 27.9±4.1          | 24.9±3.9             | 0.03    | 28.1±5.5          | 23.1±2.3             | 0.001   |
| %Total body fat                                  | 27.1±7.2          | 22.9±7.6             | 0.01    | 46.8±8.1          | 33.9±11.3            | 0.001   |
| (1) Geometric mean, p after log transformation.  | on.               |                      |         |                   |                      |         |

Table 1. Characteristics of Carriers of the N288D GK Gene Mutation and of Their Unaffected Relatives

Title: GLYCEROL AS A PREDICTOR...

Inventors: Daniel Gaudet, et al.

Table 2. Fasting plasma glycerol concentration (mmol/L) in the initial cohort of 1056 individuals, by risk factor of glucose intolerance and diabetes mellitus

|                          |             | Glycerol            | •        |
|--------------------------|-------------|---------------------|----------|
|                          | <u>N</u> o. | geometric mean ± SD | р        |
| Gender                   |             |                     |          |
| men                      | 717         | $0.065 \pm 0.081$   |          |
| women - premenopaused    | 137         | $0.071 \pm 0.093$   | < 0.0001 |
| - menopaused             | 202         | $0.099 \pm 0.085$   |          |
| Age (Y)                  |             |                     |          |
| <50                      | 486         | $0.071 \pm 0.082$   |          |
| 50 - 60                  | 408         | $0.076 \pm 0.106$   | 0.0015   |
| >60                      | 165         | $0.083 \pm 0.053$   |          |
| Fasting glucose (mmol/L) |             |                     |          |
| < 5.2                    | 449         | $0.068 \pm 0.080$   |          |
| 5.2 - 5.9                | 336         | $0.070 \pm 0.090$   | < 0.0001 |
| 6.0 - 6.9                | 271         | $0.090 \pm 0.100$   |          |
| Fasting insulin (UI)     |             |                     |          |
| <15                      | 637         | $0.067 \pm 0.082$   | 0.02     |
| <u>≥</u> 15              | 419         | $0.086 \pm 0.101$   |          |
| 2 hours glucose (mmol/L) |             |                     |          |
| <7.8                     | 572         | $0.062 \pm 0.071$   |          |
| 7.8 - 11.0               | 283         | $0.081 \pm 0.101$   | < 0.0001 |
| ε11.1                    | 201         | $0.102 \pm 0.110$   |          |
| Triglyceride (mmol/L)    |             |                     |          |
| ≤ 2.2                    | 389         | $0.057 \pm 0.062$   | < 0.0001 |
| >2.2                     | 667         | $0.082 \pm 0.103$   |          |
| Free fatty acid (mmol/L) |             |                     |          |
| < 0.6                    | 589         | $0.066 \pm 0.054$   | < 0.0001 |
| ε0.6                     | 467         | $0.111 \pm 0.112$   |          |
| Body mass index (kg/m2)  |             |                     |          |
| ≤ 27                     | 428         | $0.060 \pm 0.087$   | < 0.0001 |
| >27                      | 628         | $0.079 \pm 0.097$   |          |

p value from a one-way ANOVA

Figure 9

Title: GLYCEROL AS A PREDICTOR...

Table 3. Multivariate analysis of the relationships of fasting plasma glycerol concentration with impaired glucose tolerance (2h glucose 7,8-11,0 mmol/L following a 75 g oral load) before and after adjustment for covariates identified in

|                       | Model 1    | Model 2  | Model 3      | Model 4      |
|-----------------------|------------|----------|--------------|--------------|
| Glycerol (log)        | ,          |          |              |              |
| ß                     | 1.75       | 1.62     | 1.46         | 0.77         |
| Odds ratio            | 5.76       | 5.42     | 4.33         | 2.46         |
| p                     | < 0.0001   | < 0.0001 | < 0.0001     | 0.01         |
| Triglyceride (log)    |            |          |              |              |
| ß                     |            | 0.54     | 0.35         | 0.12         |
| Odds ratio            |            | 1.75     | 1.42         | 1.12         |
| p ·                   |            | 0.02     | 0.11         | 0.63         |
| Body mass index (k    | g/m²)      |          |              |              |
| ß                     | B <i>)</i> |          | 0.10         | ٥٥٥          |
| Odds ratio            | -          |          | 0.10<br>1.10 | 0.05         |
| p                     |            |          | < 0.0001     | 1.05<br>0.01 |
| Fasting insulin (log) |            | •        |              | 3.52         |
| B grant manual (108)  |            |          |              | _            |
| Odds ratio            |            |          |              | 0.57         |
| p                     |            | •        |              | 1.31         |
|                       |            |          |              | 0.39         |
| Fasting glucose (mn   | iol/L)     |          |              |              |
| ß                     |            |          |              | 1.13         |
| Odds ratio            |            |          |              | 2.65         |
| <b>p</b>              |            |          |              | < 0.0001     |
| Free fatty acid (log) |            |          |              |              |
| ß                     |            |          |              | 1.62         |
| Odds ratio            |            |          |              | 4.33         |
| . p                   | ٠          |          |              | 0.007        |